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SOME DIFFICULTIES IN THE USE OF THE INSULINS IN DIABETIC PRACTICE*

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IN DISCUSSING the use of the insulins with an audience of practising physicians, it would seem advisable to confine attention largely to the products commercially available at present. Only two products, *Insulin* and *Protamine Zinc Insulin*, are licensed by the University of Toronto and accepted by the Council on Pharmacy and Chemistry of the American Medical Association at the present time. However, several other varieties of greater or less merit exist which may in the future supplant these.

Difficulties in the use of protamine zinc insulin arise in large measure from the fact that its properties have not been completely mastered, as well as from the fact that many physicians have failed to distinguish protamine insulin, which is still used in considerable amounts in Europe and was used in this part of the world in an experimental way for a short time, from the later product, protamine zinc insulin.

Numerous protamines exist and their combinations with insulin yield products with specific properties. Hagedorn first found that insulin

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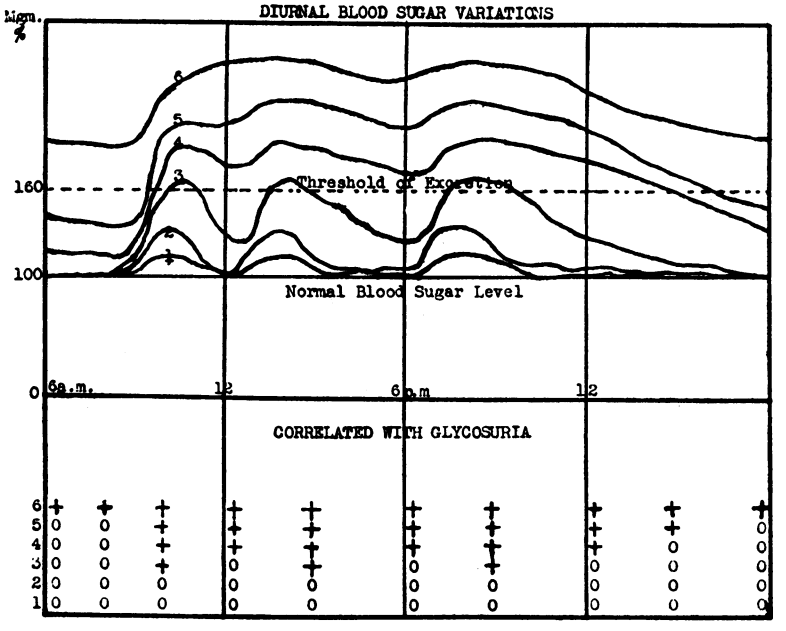

Chart I

combined with the protamine of the rainbow trout (*Salmo iridius*) had very desirable properties, a fact which was early confirmed by Joslin, Wilder and ourselves. But even more useful in certain respects was the insulin compound with king salmon protamine with which most of the experimental work on protamine insulin was carried out in America.

The investigations of Scott of the Connaught Laboratories, University of Toronto, showed a prolongation of action of insulin in animals by the addition of zinc and this we were likewise able to confirm in man, but the use of this product is accompanied by certain drawbacks. It became of great interest though to see whether or not the use of additional zinc might alter the properties of protamine insulin. Several new and very desirable properties were found to be possessed by this combination and it was made available commercially, under the name of protamine zinc insulin, as soon as adequate tests convinced us of its great value.

The first chart shows in a rather diagrammatic fashion the behavior of the blood sugar in normals and diabetics on an ordinary diet. In the normal individual there is a marked tendency to maintain the blood sugar level within certain definite limits. Nevertheless, following the

ingestion of meals, the blood sugar tends to rise somewhat for a short period and then to revert to a lower level within the normal band. Curves 1 and 2 are supposed to illustrate the fact that this is a variable phenomenon in different people. Seldom does the postprandial rise in normal individuals pass beyond .145 per cent. During the remainder of the twenty-four hours the blood sugar lies within the normal band. In other words, the normal variations in blood sugar do not pass beyond the level of the threshold of excretion, usually .160 per cent or a little higher, and no glycosuria results, as is indicated below. Glycosuria would result, however, if this threshold were lowered, producing the so-called renal glycosuria; and the greater the lowering of this threshold the more constant the glycosuria becomes. Occasionally this glycosuria cannot be stopped except by forcing the blood sugar to excessively low levels but, of course, this is never done as a practical measure of control. Renal glycosuria is a benign condition, an anomaly, requiring recognition rather than treatment. In Curve No. 3 we find the blood sugar starting within the normal values and rising after meals to overstep the threshold of excretion, glycosuria resulting at these times but disappearing as the blood sugar falls back to normal levels. This patient furnishes us with many problems. Numerous causes may produce this result: alimentary hyperglycemia, obesity, infection, liver disease, a lag type curve. But sometimes the patient is the mildest type of diabetic and peculiarly important because at this stage early strict treatment may wholly arrest the progress of the condition while he still has a high tolerance for carbohydrate or, perhaps, even bring about a cure. Curve 4 also starts within normal blood sugar limits but it rises above the threshold after a meal and continues thus, perhaps falling slightly before the next meal but rising again soon after this has been taken. After absorption of the evening meal the blood sugar falls to normal and remains so during the night. This patient is a mild diabetic, probably readily controllable by dietetic measures, but he introduces the question as to how much value he might gain from a period of support by a small supplement of a long acting insulin. Curve 5: Well marked fasting hyperglycemia with an increase above the threshold level after meals and long continued glycosuria, only ceasing during the night, is a stage of greater severity of diabetes, sometimes controllable by rigid dietary restrictions, and often benefited by small doses of insulin. In Curve 6 we have depicted the blood sugar level continuously above the

threshold level and constant glycosuria—a definite diabetic who will almost certainly require insulin to assist in metabolizing a suitable diet.

In connection with Chart I there are several points to be noted: a diabetic is not always continuously glycosuric; diabetes is not the most frequent cause of glycosuria; literally hundreds of other causes may operate but diabetes is the most constant and the most persistently recurrent cause of hyperglycemia and glycosuria as well as the probable cause of maximal deviations from normal values. Diabetes varies in severity. Besides other features which may often assist in diagnosis, both hyperglycemia and glycosuria either constant or persistently recurrent, are necessary for the diagnosis in most cases.

Chart II: All diabetics do not need insulin. When placed on restricted diet the mild diabetic promptly becomes sugar free. Some patients, however, become aglycosuric with greater difficulty and only after some days. Perhaps they may require insulin to assist in metabolizing more liberal diets required for their daily work. A third group will not become sugar free, and insulin definitely is necessary for these patients. A test period on restricted diet would eliminate many of those cases now placed unnecessarily on insulin and later found not to require it. I am not unmindful of the fact that in certain instances insulin administered to mild and early cases may sometimes be of value in ameliorating their severity, but on this subject too little data now exist. Their recognition is largely dependent upon adequate preliminary testing of their tolerance. In such a group with high initial tolerance there will be few difficulties to overcome in connection with the administration of insulin. One recognizes the greater stability of the normal individual to a given dose of insulin; these mild diabetics resemble normal individuals in this respect more than the severe cases of diabetes mellitus.

Reference to our early work on insulin will indicate that such insulins did possess a more prolonged action than the regular type now available commercially. Through the years, as purity of the product was increased, the action became more explosive, as it were, and an increasing number of doses was required to manage severe cases of diabetes. Whether the original long action was due to their high zinc content, which Scott has shown definitely prolongs the action of insulin, or to other adjuvants now refined out of the product, is not now known, but one may contrast the twenty-four hour action of early insulin, as shown in Chart III Curve 1, with the more rapid action of

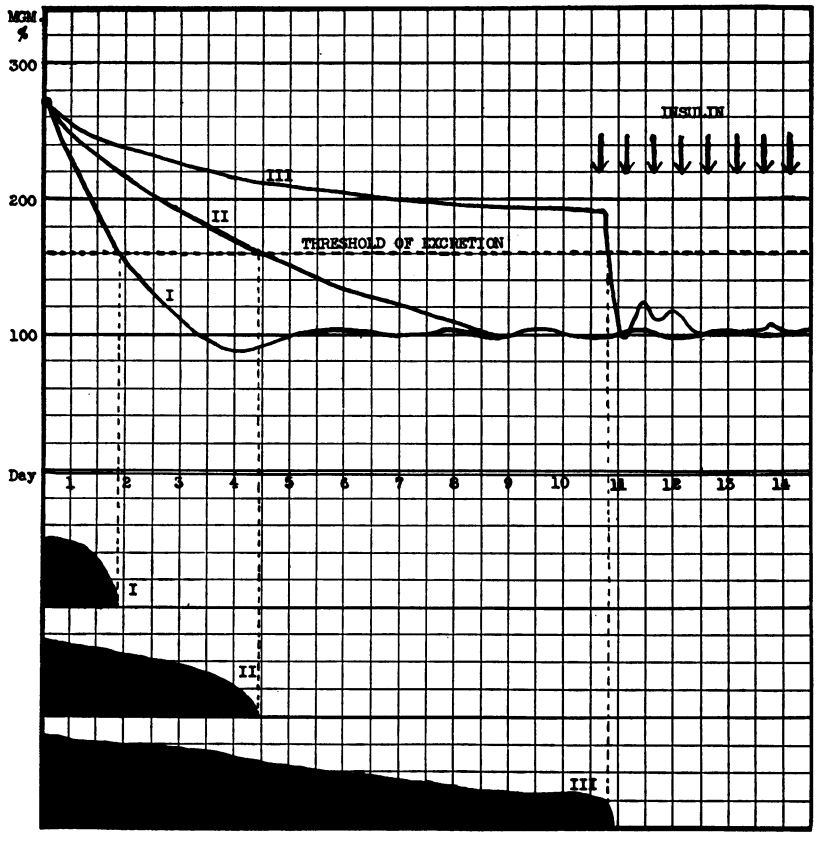

Chart II—Hyperglycemia and glycosuria in: I, mild; II, moderately severe; and III, severe diabetics under treatment.

1936 insulin in Curve 2. In the latter, the action is wholly completed before the older preparations had caused their maximum fall of blood sugar.

The third curve on Chart III shows the effect of an equal dose of Hagedorn's salmaridin protamine insulin in the same individuals. As will be noted, the action is more gentle and more prolonged than that of the unmodified preparation. Without doubt the modification of insulin by means of protamine and other substances has made possible the greatest improvement in diabetic treatment since the introduction of insulin itself.

How, then, does protamine zinc insulin differ from ordinary or unmodified insulin? I have endeavored to answer this in part in Chart

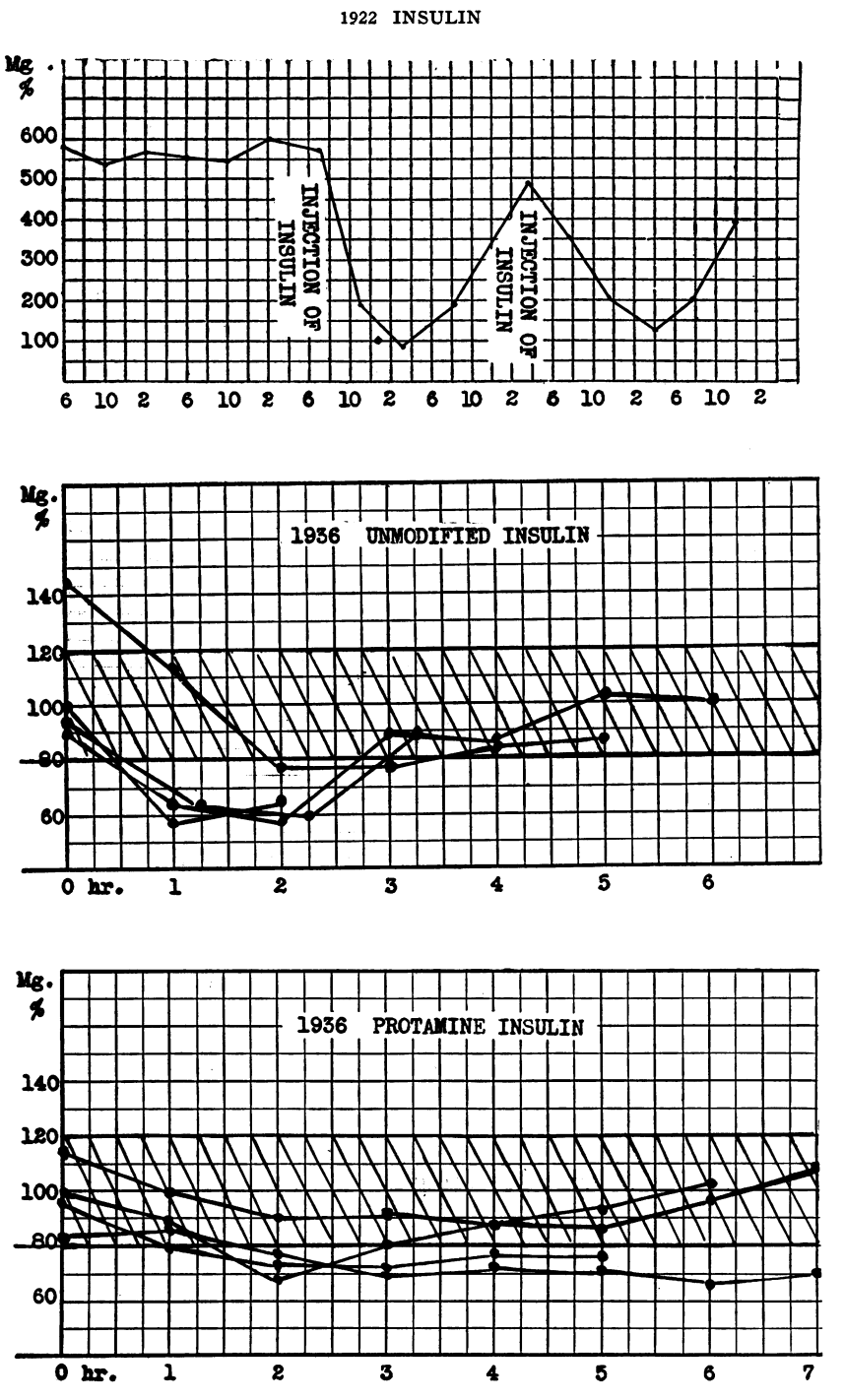
1922 INSULIN
Mg. %
600
500
400
300
200
100
INJECTION OF INSULIN
INJECTION OF INSULIN
6 10 2 6 10 2 6 10 2 6 10 2 6 10 2 6 10 2
Mg. %
1936 UNMODIFIED INSULIN
140
120
100
80
60
0 hr. 1 2 3 4 5 6
Mg. %
1936 PROTAMINE INSULIN
140
120
100
80
60
0 hr. 1 2 3 4 5 6 7

Chart III

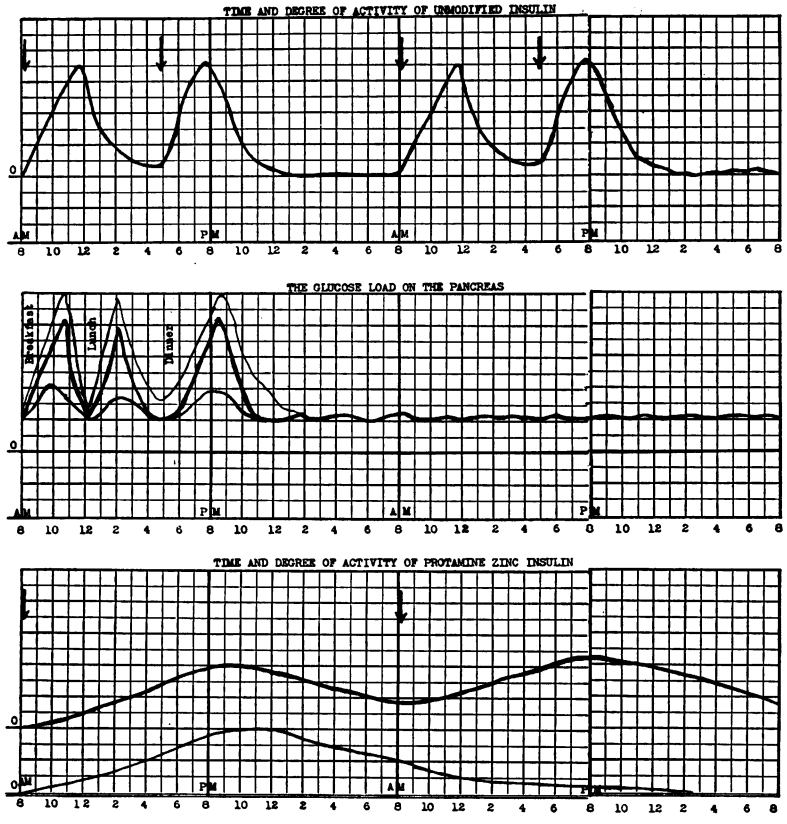

Chart IV

IV. Regular insulin is a solution and when injected is rapidly absorbed and available early to do its work but, as you will have noted previously, its action is now of short duration. If we allow the squares of Curve 1 to represent some hypothetical unit of efficiency, then the curve of insulin activity outlines the amount of work performed and we see that the diabetic given two doses of such an insulin in a day gets rapid large effect which is completed early, and during the night hours the patient is left dependent upon such insulin as he can produce himself. Quite probably, if the carbohydrate intake is not excessive, the pancreas supplies but little insulin during the period of action of the injected insulin and a greater amount of the patient's own insulin is available for the night hours. It is also true that during fasting or during the night a comparatively small amount of insulin is required but the relatively small store of glycogen soon is used up. The patient falls back on

protein utilization to obtain the necessary energy to live and by morning the blood sugar of the patient rises to abnormal levels unless suitable further injections are introduced or unless the patient has sufficient insulin production of his own to counteract this process. In other words, in the case of patients with small insulin production or patients on high calory or high carbohydrate diets with unmodified insulin, the diabetic tendency is mastered for only a few hours of the day; the remainder of the time he is only a little less diabetic than before. Particularly is this true of patients who are allowed to have high blood sugar or a little glycosuria as often has been done, allegedly to protect them from the dangers of nocturnal reactions.

Before contrasting these effects with those of protamine zinc insulin, we may examine Curve 2, which represents what I conceive to be the normal distribution of the glucose load on the pancreas, meaning by this not only the absorbed carbohydrate as such but also that derived from the glycerine of fat and the breaking down of protein. The starting point of the curve, being somewhat above the zero line, is intended to represent the fact that some insulin is required normally for endogenous metabolism even during fasting. However, immediately the carbohydrates from the meals commence to be absorbed, this load is increased in degrees varying with the amount absorbed. Following the absorption of food the load falls to a lower level which persists throughout the night. Now, comparing this curve with Curve 1, we see that regular insulin is most usefully employed to counteract the effect of the ingested carbohydrate. The more effectively these two factors are balanced, the better the patient's own insulin can be used to maintain a normal state during the night. In many cases this has been found to be actually insufficient and small supplementary doses are required to keep the patient normal during this period. It is apparent, then, that a longer acting insulin would be desirable to reduce the number of doses of insulin required and to maintain the normal metabolism of the patient for a longer period of time.

Salmaridin protamine insulin provided a partial answer to these requirements, being effective in maintaining normal metabolism for some sixteen hours. Onchorhynchin protamine insulin was effective for some twenty-two hours. Chart III indicates that the zinc modification of onchorhynchin protamine insulin has a still longer effect. Taking the lower line, the curve indicates that, though the slow absorption of the

suspension of this product makes a high degree of activity impossible, the activity is continued in useful amounts for some thirty hours. Indeed, Wilder has shown that some activity is present for fifty-seven hours; similarly my colleague, Dr. Fletcher, has obtained evidence that a minimal degree of activity persists for some sixty hours during partial fasting. The upper curve represents the fact that the effect of successive daily doses of protamine zinc insulin is cumulative to some degree. Yesterday morning's insulin helps to provide in part for the metabolism of today's breakfast.

Comparing the action of this insulin with the glucose load on the pancreas, Curve 2 indicates that it will be most effective in balancing the constant load of the endogenous metabolism on the insulin-producing mechanism rather than in ironing out the peaks in the curve induced by the absorption of food. *The maximal useful dose of protamine zinc insulin is that which leaves the patient with a low normal fasting blood sugar without nocturnal hypoglycemia.* By this means he attains the largest margin between the fasting blood sugar level and the threshold of excretion after breakfast, and somewhat better rest for the pancreas during the night so that any self-manufactured insulin may be devoted to controlling the absorptive hyperglycemia. Possibly this rest accounts also for the slow reduction in insulin requirement noted in so many cases. As the new injection of insulin is gradually absorbed and reaches its maximum level, larger amounts of carbohydrates may be placed in the later meals of the day. However, protamine zinc insulin alone is ill adapted to the consumption of high carbohydrate diet and any hyperglycemia or glycosuria encountered is very slowly controlled. One may attempt to counteract this, as well as the tendency to nocturnal hypoglycemia because of overdosage of insulin, by putting a portion of the carbohydrates into a bedtime lunch, but this procedure is not entirely satisfactory. Prolonging the digestive and absorptive period by suitable selection of food may lower the peak of the load and permit the use of 5 to 8 units of more long-acting insulin. This may be done in suitable cases by using unripe bananas, by smothering berries or peaches with cream, by using heavy cream or butter on oatmeal or puffed cereals, by using fat meats, French-fried potatoes and French sticks or Vienna rolls liberally spread with butter. With long-acting insulin the problem of evening refreshments can be solved safely by taking a supper somewhat lower in carbohydrate than usual and selecting suitable refresh-

ments. One of my patients, whose severe diabetes remains unknown to his associates for business reasons, has made himself popular with hostesses by his activities in serving the evening refreshments. No one ever notices that he has no time to eat more than a small sandwich, a few nuts, or drink a cup of coffee. If it appears necessary to take more, he walks home "to clear his head of the smoke." The walk uses up a little more carbohydrate. He has never had glycosuria or hypoglycemia since going on protamine zinc insulin nearly three years ago.

It must be clear that protamine zinc insulin has but a limited capacity to take care of ingested carbohydrate and that treatment is more successful with the lower carbohydrate diets than with those containing a more liberal amount. Roughly, it may be said that severe diabetics cannot take a diet exceeding 100 grams of carbohydrate (or 150 grams total glucose) while using a single morning dose of protamine zinc insulin. An attempt to do so results in glycosuria, hypoglycemia or both. With diabetes of lesser severity a larger amount of carbohydrate can be utilized by giving the protamine zinc insulin in amounts sufficient to produce a low normal fasting blood sugar without hypoglycemia and utilizing the remaining pancreatic efficiency to counteract the postprandial hyperglycemia and glycosuria. Successful treatment, according to my criteria—adequate caloric intake and maintenance of the blood sugar within normal limits—becomes more and more difficult to attain as the carbohydrate in the diet rises, but sometimes is accomplished if the total calories can be kept low. Amounts of carbohydrate much above 150 grams, in my opinion, are usually unwise unless it is necessary to provide more because of failure of lipase secretion by the pancreas. Many patients on diets containing 250 grams of carbohydrate would be better on a lower carbohydrate ration without insulin.

In the fasting state the slowly absorbed insulin is definitely more economical than regular insulin. Fewer units are required and in addition hypoglycemia is not so much to be feared. If calories are allowed at a working level, this economy diminishes as carbohydrate in the diet increases. When the carbohydrate of the diet is below 100 grams, 60 per cent as much protamine zinc insulin as regular insulin will be equally effective. At 100 to 125 grams of carbohydrate, 75 per cent as much protamine zinc insulin as regular insulin will be required. But little economy is observed when more than 150 grams of carbohydrate are given in a working diet. On the other hand, if undernutrition diets are

prescribed, considerable economy is observed with somewhat larger carbohydrate allowances.

To many, the plan of giving protamine zinc insulin in small and gradually increasing doses from the beginning of treatment commends itself, especially if ambulatory treatment is necessary. There are numerous advantages in commencing treatment under hospital conditions, however. In this case it seems preferable to determine whether the patient can metabolize a basal diet and then increase the food allowance in ladder fashion towards the maintenance level, using regular insulin, if necessary, as the required period of observation is far shorter than if protamine zinc insulin is used. In transferring patients from regular insulin to protamine zinc insulin, doses up to 75 units per day of the unmodified insulin are substituted by 60 per cent as much protamine zinc insulin given in a single morning dose. However, since the insulin from this injection is absorbed slowly, it is probable that glycosuria may occur prior to the insulin becoming available. To obviate this, 60 per cent of the balance of the original dose of regular insulin is given with the first dose of protamine zinc insulin and the remainder of the regular insulin before the evening meal. On the following day, the morning dose of protamine zinc insulin is accompanied again by regular insulin, as before, but thereafter it is discontinued.

If a patient attains a low normal fasting blood sugar level without nocturnal hypoglycemia on a given dietary regime, but shows glycosuria, examination of urine collected every two hours is indicated to determine the time of the glycosuria. Onset of glycosuria, not duration, is the more important, though large increases in glycosuria following the later meals are also significant. Not infrequently some rearrangement of amounts of carbohydrate in the various meals may cause the glycosuria to disappear. Spreading the meals over a larger number of hours or smothering the carbohydrate in fat, as suggested by Pollack, may be tried, or even a bedtime lunch which may make possible a few more units of insulin without inducing hypoglycemia. Should these measures fail, one is faced with the alternative of using less carbohydrate in the diet or of reinforcing the action of the protamine zinc insulin and of the pancreas with some regular insulin. With severe diabetics reinforcing with regular insulin nearly always will be required, as also is usually the case when very high carbohydrate allowances are made without shrinking the total calories. Regular insulin should be adminis-

tered in addition to the previous dose of protamine zinc insulin at first, though later it is probable that the protamine zinc insulin may be reduced somewhat. Preferably, regular insulin should be given in the morning, close to breakfast time, and it is most convenient to give the protamine zinc insulin at the same time. With protamine zinc insulin, as opposed to the more rapidly acting protamine insulin, there is comparatively little to be gained by shifting the time of injection by one or two hours, so that giving it with the breakfast does not matter except as a minor inconvenience to the patient.

Attention should be called to a detail which sometimes is neglected. Adjustment of the insulins to the requirement of the resting individual is frequently not the most satisfactory for the working individual. The perfectly adjusted hospital patient frequently has difficulty with hypoglycemia on his return to working conditions. I feel that there is little doubt that gradual increases in the diet to a working level give the most satisfactory results in treating the diabetic but, in approaching the working level of the diet from below, it is desirable to arrange increases in activity, such as walks or occupational therapy, to simulate the working conditions of the patient and thus avoid abrupt alteration of conditions on discharge from hospital. A little more attention to this point would avoid many of the difficulties and disappointments now being experienced with protamine zinc insulin.

An occasional cause of glycosuria and, later, hypoglycemia may be the failure of the patient to observe the caution to mix thoroughly the suspension of protamine zinc insulin in the bottle before removing the dose. Neither insulin should ever be injected intramuscularly because of the injury to muscle tissue, and protamine zinc insulin should not be injected intravenously as most of the prolonged effect is lost and the patient is subjected to a certain amount of danger from the protamine itself.

It may not be amiss to point out here that when we were working with protamine insulin I introduced the method of layering the two insulins in the same syringe and injecting them through one skin puncture in two places under the skin. This was a convenience but is not possible with protamine zinc insulin. For stabilization purposes, protamine zinc insulin contains both excess protamine and excess zinc so that, if mixed in the tissues, all will become protamine zinc insulin. However, it is still possible to avoid the pain of a second skin puncture

by using three-quarter inch needles and two syringes. A needle is attached to the syringe containing regular insulin, plunged far, but not deeply, under the skin and the contents injected; the needle is almost withdrawn, its direction changed, and again inserted to a point some distance from the original injection; the empty syringe is now removed, a syringe containing protamine zinc insulin substituted and its contents injected.

The more severe the diabetes, and the higher the carbohydrate content of the diet, the more likelihood there is that more than one daily dose of insulin will be required. In my experience, when more than 50 units of protamine zinc insulin are required, it is comparatively seldom that the long acting insulin alone will adequately control the patient's metabolism. In such instances the change-over morning dose of regular insulin, mentioned above, may be continued and usually it will be found advisable within the next few days to reduce the protamine zinc insulin to 50 per cent of the amount of regular insulin originally used. No absolute rule can be laid down, however, since results are so much dependent upon the original tolerance of the individual, the total calories and the proportion of the diet made up of carbohydrate substances. The useful dose of protamine zinc insulin is limited by the production of nocturnal hypoglycemia. This must be avoided. At the same time, it is desirable to use sufficient protamine zinc insulin to ensure a low normal fasting blood sugar in the morning. From this basis the appropriate amount of regular insulin may be worked out by watching the postprandial hyperglycemia and glycosuria. Experiments have been made giving the protamine zinc insulin at various times of the day, and sometimes these are successful. Administration of protamine zinc insulin at eleven o'clock at night, so that its maximal action occurs around breakfast time in the morning, occasionally has some advantages. However, it frequently results in hypoglycemia before breakfast. Administration of two smaller doses, morning and evening, may result in utilization of more carbohydrate although it does away with the convenience of a single injection. With some few patients it may be necessary to give protamine zinc insulin in the morning together with regular insulin, and to administer a second dose of regular insulin later in the day in order to keep the patient free of glycosuria. In these cases I have noticed that this usually is a temporary requirement and that later, presumably because of the benefits of rest to the pancreas, the evening dose can be

discontinued. Of course, the state one wishes to attain is that of an adequate diet with a normal blood sugar throughout the twenty-four hours; a considerable amount of experimentation, both with dietary regimens and insulin dosage, is sometimes required to attain this in instances of maximal severity. The twenty-four hour blood sugar curve, though much used by us, is not necessary for routine treatment. A low normal fasting blood sugar, a blood sugar of .145 or below at 10:30 A.M. and freedom from glycosuria or hypoglycemia throughout the day will ensure that no gross deviations occur.

In no case is the abandonment of protamine zinc justified by its failure to do what it may legitimately be expected to do if its powers and limitations are fully understood. The trouble lies with the lack of knowledge or therapeutic resource of the physician or with what one may call the idiosyncrasies of the patient. The latter, of course, cannot be left out of consideration, but the ultimate benefits to be derived from protamine zinc insulin alone, or in combination with regular insulin, are worth considerable study in every case.

I suppose everyone would desire an amelioration of the dietary restrictions of the diabetic. In this connection the considerable advantage of being able to combine in one solution a rapidly acting insulin and a more slowly acting factor, capable at once of combating absorptive hyperglycemia and of controlling the endogenous carbohydrate metabolism of the body apart from meals, has not escaped notice. Numerous experiments have been made with this object in view but, unfortunately, I can give you no idea when such a product may become available. Work of this sort is time-consuming and many failures are to be expected before the adequate solution is attained.

The effect of infections on the patient using protamine zinc insulin is somewhat variable. We believe that thorough treatment of diabetics tends to raise their resistance to infections toward the normal and so lower the incidence of infections which become of clinical importance. With regular insulin it is well known, however, that in severe infection the usefulness of the insulin is materially diminished and non-recognition of this fact may be responsible for development of acidosis and even of coma in these patients. With protamine zinc insulin the rate of absorption of the insulin and the rate of action is much slower and toxic effect on insulin efficiency, however it is brought about, is decidedly more marked. As part of their training, diabetic patients should be

warned to consult their physician immediately upon the development of any infection and appearance of either glycosuria or ketonuria. In treating these patients I prefer to leave the dose of protamine zinc insulin unchanged and add regular insulin in small, frequent doses to supplement its effect, reducing the unmodified insulin dose, of course, as the need for it subsides. In initiating diabetic treatment in a patient with an infection, one would prefer the use of regular insulin for its more rapid effects. As an adjunct to regular insulin, however, some use what may be called a sustaining dose of protamine zinc insulin and believe it to be of benefit to the patient.

There is some conflict of opinion on the use of protamine zinc insulin in relation to surgical operation. Some prefer it to regular insulin. If the patient already is using protamine zinc insulin, I would not discontinue it but would supplement the dose with regular insulin and glucose preoperatively, watch for evidence of acidosis following operation and, if necessary, use supplementary doses of regular insulin to combat it. Diabetics not requiring daily insulin otherwise should receive regular insulin and carbohydrate before operation unless their carbohydrate tolerance is high. Postoperatively, a sustaining dose of protamine zinc insulin is hardly necessary and, in order to avoid a later hypoglycemia, is inadvisable unless glucose is being administered intravenously at the same time. For an emergency operation because of infection protamine zinc insulin is useless, being too slow in its immediate effects. There is, possibly, something to be said for a sustaining dose administered before operation for use in the postoperative period, when glucose is being administered intravenously but, as an emergency due to the toxic factor destroying the insulin must be met with regular insulin in any case, I prefer to avoid the complicating factor and use regular insulin alone.

Acidosis in the diabetic patient is still too frequent. As a complication of infection it probably occurs more often in the patients treated with protamine zinc insulin than in those treated with regular insulin. It should be treated by adding regular insulin to the protamine zinc insulin treatment. When induced by neglect of treatment, or improper dietary control, the quickest way to bring it under control is by the use of regular insulin. Should an occasion arise when it is desirable to control a mild acidosis without creating alarm, orange juice and other fluids and liberal doses of protamine zinc insulin probably will be effective and

may be reinforced by regular insulin at any time, if necessary. Protamine zinc insulin will do the work if time is available. However, it is not always wise to allay the alarm of the careless patient and his neglectful relatives.

Coma is an emergency and should be treated as such. Today patients die, not of coma, but of the circulatory failure induced by coma. Properly treated with large doses of regular insulin, they should be out of coma before any considerable effect could be expected from protamine zinc insulin. To smooth the course of the immediate after-treatment and to prevent protein breakdown between periods of activity of the regular insulin, a dose of protamine zinc insulin administered early might serve a useful purpose. But if sufficient regular insulin is being used to ensure maximal conversion of metabolism to a carbohydrate type, it is difficult to imagine any occasion for its employment.

When Fletcher and I first described the clinical syndrome hypoglycemia, we felt it of the utmost importance to impress on those using insulin the dangers of the new drug. Insulin hypoglycemia is still dangerous but, in most instances, not to the degree we had anticipated. Today, insulin hypoglycemia, when induced by protamine zinc insulin, is dangerous in comparison with regular insulin, but the number of reactions is cut down materially. The danger lies partly in the insidious onset of hypoglycemia and in the tendency to recur when once cured with soluble carbohydrate. The older symptoms were associated with speed in the fall of the blood sugar; the newer insulin often steals away the blood sugar so gradually as to excite almost no symptoms until severe reaction levels are attained. Also, even with the immediate reaction cured, the remaining unabsorbed insulin on entering the blood stream may cause repetition of the reaction some hours later. While the well-known symptoms are encountered in some cases, hypoglycemia with the new insulin is often accompanied by a sensation of undue fatigue, negativism, slight headache or nausea and evidences that the normal repressions are lacking. Signs of deficient cerebral control, as in mild alcoholic intoxication, are more prominent features of the new picture. Somewhat greater difficulty is experienced in controlling reactions which have progressed to this blood sugar level but soluble carbohydrate administered by mouth is effective usually and can be reinforced by intravenous glucose if necessary. Until some starchy food is obtainable, soluble carbohydrate in small doses should be repeated each thirty

minutes. Bread and honey or bread and corn syrup form an effective antidote both for the immediate relief of the patient and for his protection against a subsequent attack when more insulin has been absorbed into the blood stream from the site of injection.

Unless precipitated by gross overdosage, fasting, indigestion, diarrhea or unusual and excessive exercise, reactions due to protamine zinc insulin administered in the morning will occur after six o'clock in the evening. With protamine zinc insulin, a reaction due to exercise may be delayed for many hours. Therefore, marked variations in the routine of living from one day to another should be avoided as much as possible to minimize this risk. When both insulins are being used in the morning, any reaction due to regular insulin will occur during the day and if a supplementary dose of regular insulin is used at supper time, a reaction due to it will occur before midnight. While not invariable, these rules indicate which insulin may require reduction. Not less than five units should be removed from a protamine insulin dose while two units reduction may suffice to abolish hypoglycemia from the regular insulin.

Local swelling due to the injection of protamine zinc insulin continues longer than that from unmodified insulin and may cause more prolonged discomfort. Sensitization reactions sometimes appear with increased local swelling: edema, urticaria, pruritus and even general symptoms may occur on rare occasions. In my own experience these have been usually of minor importance and were allayed by cold compresses or by allowing a saturated solution of magnesium sulphate to dry on the skin. Spontaneous desensitization usually will occur in two to three weeks if treatment is continued. More severe degrees of sensitization occur in patients who are already sensitive to the protein of the species from which the insulin is derived or in patients who have discontinued the use of insulin at some previous time. These are due usually to sensitization to the accompanying traces of species' protein but occasionally are due to insulin itself. When due to protein sensitization, another preparation of protamine zinc insulin may be tried or the patient may be given regular insulin derived from another species for a time, then gradually desensitized by substitution of small, but gradually increasing, doses of the offending insulin. Alternatively, crystallized insulin may be used and gradual desensitization carried out. If the patient is sensitive to insulin itself, he may be placed on an under-nutrition diet and desensitization carried out with crystallized insulin, either by the

Besredka or by the slow method, injecting the insulin in approximately the same spot repeatedly, as local desensitization precedes the general process.

Though antigenic properties of protamines have been denied, some cases of sensitization have been stated to occur. It is far from clear that they are not due to slight traces of accompanying fish protein rather than to the protamine itself. We have failed thus far to encounter this difficulty which doubtless could be surmounted by placing the patient on unmodified insulin temporarily and desensitizing with small doses of protamine zinc insulin or pure protamine solutions.

The greatest source of difficulty with protamine zinc insulin is impatience. This insulin is slow acting and cumulative and time is required for its full action to develop. Premature increase in the dose to hasten the action results in hypoglycemia, though on the same day the patient may have had glycosuria from the carbohydrate of the meals. Not less than four to seven days on a certain regimen is adequate to determine whether it is satisfactory, though it may be possible in shorter time to determine that a program is unsatisfactory. Hasty conclusions on this point should be avoided.

Finally, with adequate preliminary investigation and control, all diabetic patients requiring insulin will do better on protamine zinc insulin, or on a combination of protamine zinc insulin and regular insulin. No suggestion that a complete solution of the problems of the most severe and unstable cases of diabetes has been accomplished is warranted but we have been gratified to find that better control of such cases may be obtained by the use of protamine zinc insulin than was previously possible and many are markedly improved. For those with a lesser degree of severity, one may say there is an improvement in their general health, a reduction of the number of doses, economy of insulin, improvement of the twenty-four hour blood sugar level, and superior control of azoturia and ketonemia. There is also a diminution in the frequency of reactions though, when these do occur, they may be more difficult to diagnose and treat effectively. The patient has much greater freedom of action, and there are numerous indications that a slow but very definite improvement of tolerance occurs in some cases. Protamine zinc insulin has multiplied the problems of the physician treating the patient but for the latter, when he has been successfully stabilized, the outlook is improved immeasurably.